REMARKS

Reconsideration of the application is respectfully requested.

Claims 2, 5-8, 14, 21, 24-27, 32, 38, 39, 41-44, and 47-50 have been canceled without prejudice or disclaimer. Claims 11-13, 15-19, 29-31, 33-37, and 40 have been withdrawn from consideration.

Claims 1, 3, 20, 22, and 45 have been amended to clarify the claimed subject matter and correct claim dependency. Support for the claim amendments is found in the claims as originally filed and throughout the published specification, for example, at col. 4, ¶ 26.

No new matter has been added. Upon entry of this amendment, claims 1, 3, 4, 9-10, 20, 22, 23, 28, 45, and 46 are pending and at issue.

Election/Restriction

The Examiner acknowledged Applicants' election of "Group I" claims in response to the restriction requirement mailed October 19, 2007. However, the Examiner states that because SEQ ID:4 is not recited in independent claims 1 or 20, some of Applicants' originally elected claims do not read on SEQ ID NO:4 and have therefore been withdrawn from consideration (claims 5-8, 11-19, 24-27, 29-37, 40-44, and 47-40 have been additionally withdrawn by the Examiner) (*see* Office Action, page 2).

By way of this amendment, independent claims 1 and 20, have been amended to recite compositions comprising elk prion proteins, i.e., proteins of SEQ ID NO:4. Therefore, claims 11-13, 15-19, 29-31, 33-37, and 40 read on elected species SEQ ID NO:4.

Enablement Rejections

Claims 1-4, 9, 10, 20-23, 28, 38, 39, 45, and 46 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. According to the Examiner, claims 1 and 20 broadly encompass all mammalian prion proteins, including human proteins. The Examiner states that the specification does not enable the induction of a protective immune response (i.e., prophylaxis) against prion diseases in humans, and that regardless of the data presented for mice, undue experimentation would be required to enable the claimed invention in humans and other animals (*see* Office Action, pages 4-6).

Claims 2, 21, 38, and 39 have been canceled without prejudice or disclaimer, thereby rendering this rejection moot as to these claims.

Without conceding the validity of the rejection, and in order to advance prosecution of the present application, claims 1, 20, and 30 have been amended, without prejudice or disclaimer, to recite compositions comprising a mammalian prion protein and an antigen carrier or delivery vehicle, wherein the mammalian prion protein is bovine, deer, elk, or sheep. Support for these amendments is found in original claims 2, 21, and throughout the specification. Therefore, the presently claimed invention does not encompass compositions comprising human prion proteins, thereby rendering this basis of the rejection moot. By way of these amendments, Applicants are not abandoning compositions that comprise human or other mammalian prion proteins, and maintain the right to pursue one or more applications wherein compositions comprising such prion proteins are claimed.

With respect to the presently claimed prion proteins, Applicants traverse the rejection and respectfully request reconsideration.

The test for adequate enablement is whether one skilled in the art could make and use the claimed invention from the disclosure, coupled with information known in the art, without having to resort to undue experimentation. *United Stated v. Telectronics, Inc.*, 857 F.2d 778, (Fed. Cir. 1988). The test of is not whether *any* experimentation is necessary, but whether, if

experimentation is necessary, it is undue. *In re Angstadt*, 190 USPQ 214 (CCPA 1976) (emphasis added). Importantly, an extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance in the specification. *In re Colianni*, 195 USPQ 150 (CCPA 1977). Applicants submit that based on the guidance provided in the instant disclosure, what was known in the relevant art at the time the application was filed; and the capabilities of a person of ordinary skill in the art, undue experimentation would not be required to make and use the presently claimed invention.

A. Disclosed Mouse Model Provides Adequate Guidance and Predictability for other Mammals

The Examiner acknowledges that the specification provides working examples that demonstrate generation of mucosal immune responses in mice immunized with *S. typhimurium* that comprise cDNA that encodes prion protein (*see* Office Action, page 5). However, the Examiner contends that a skilled artisan would have to conduct undue experimentation in order to reasonably conclude that the claimed compositions could prevent prion infection in animals other than mice. *Id.*

Applicants submit that the Examiner's position is not well founded for several reasons. First, the working Example noted by the Examiner (example 2) provides adequate guidance to a person of ordinary skill in the art regarding: **i**) preparation of the claimed compositions; **ii**) mucosal (gastric) immunization of animals; **iii**) antibody measurement preceding and subsequent to mucosal immunization; and **iv**) immune system assessment at the end of the experiment. Example 4 describes another working example wherein mice were orally inoculated with *Salmonella* bacteria transfected with genes encoding prion proteins, and after inoculation with scrapie, the mice were monitored for clinical signs of the disease. These working examples provide ample guidance for a person of ordinary skill in the art to make and use the invention in mice, but also, in other animals such as deer, elk, sheep, and cattle.

It is well known in the immunological field that mouse models provide excellent tools for predicting and studying immune responses in other animals. Mice are often the preferred models of investigation in the biological sciences because of their ease of acquisition and handling, cost of maintaining, rates of reproduction, and so forth.

Although the Examiner contends that mouse studies are not predictive of results in other animals, this position is contradicted by what has been published regarding the utility of mouse models in the study of immunology generally, and prion diseases specifically.

Mouse models are also widely recognized and relied upon in prion disease research. Applicants attach a review of prion therapeutic experimental models (Trevitt, et al.) (**Attachment A**) wherein the authors disclose that "The central feature of prion diseases is the accumulation in the brain and some other tissues of the disease-associated PRP^{Sc}," which can be "extracted from diseased brain tissue as aggregated material" (*see* Trevitt, page 2242, first paragraph). Because of the pathologic similarity of prion diseases between rodents and other animals, mice became a significant tool in the evaluation of the disease and therapeutic approaches. Trevitt states that "perhaps the most promising of these [previously discussed therapies] for treating human prion disease is passive immunization with anti-PrP antibodies, which has been shown to prevent progression of peripheral prion infection to neurological disease in mice" (*id.* at page 2259, first full paragraph). The article notes that "Several groups have reported moderate beneficial effects of active immunization of mice with prion protein or peptides prior to infection with scrapie isolates" (*id.* at page 2253, col. 2).

Applicants also attach a review article that discusses the molecular mechanisms of prion pathogenesis (Aguzzi, et al., *Annu. Rev.Pathol. Mech. Dis.*, 3:11-40 (2008) (**Attachment B**). Aguzzi provides ample disclosure relating to the similarity of prion disease in mice and higher animals such as ruminants (e.g., sheep goat, cattle, elk, and deer) and humans. First, Aguzzi teaches that prion diseases in various species have a fundamental characteristic, i.e., the aggregation of aberrantly folded prion protein into large amyloid plaques and fibrous structures associated with neurodegeneration. "The cellular prion protein (PrP^{C}) is absolutely required for

disease" (*see* Aguzzi, abstract). In this regard, Aguzzi further states that "mature PrP^C from mouse, human, cattle, and Syrian hamster share common [structural] features" (*see* Aguzzi, page 13, last paragraph) and that "PrP^C is a highly conserved protein in mammals" (*id.* at page 15 second paragraph). It is chiefly because of the similarities in prion pathology and protein homology that mouse models serve as a useful model in higher mammals and are routinely relied upon by skilled artisans.

This position is supported by the extensive use of mouse models in prion protein research and the correlation of findings in mice to results seen in other animals. For instance, in describing experiments regarding the role of PrP, Aguzzi discloses:

> ...the brain, blood, and heart of GPI-negative transgenic mice contained both abnormal and protease-resistant prion protein as well as prion infectivity. Blood plasma of GPI-negative transgenic mice was found to be infectious...*mimicking a situation of blood-borne prion infectivity as known from scrapie sick sheep, chronic wasting diseased elk and deer, and vCJD [human] patients.*
>
> *Id.* at page 23, col. 2, first full paragraph (emphasis added).

Aguzzi, in discussing the pathogenesis of prion diseases, discusses the role of follicular dendritic cells ("FDCs"). The review states:

> The importance of FDCs in peripheral prion pathogenesis may be exploited for prion prevention strategies. Inhibiting the lymphotoxin beta receptor (LTβR) pathway in mice *and* nonhuman primates by treatment with LTβR-immunoglobulin fusion protein results in the disappearance of mature, functional FDCs.
>
> *Id.* at page 25, col. 1, second paragraph (emphasis added).

The correlation between mice and higher mammal prion disease is demonstrated when Aguzzi states:

> The detection of PrPSc in spleens of sCJD [human] patients suggests that the interface between cells of the immune system and peripheral nerves

> might also be of relevance in sporadic prion diseases. Indeed, *in mouse scrapie studies*, there is no doubt that the microarchitecture of lymphoid organs crucially controls the efficacy of prion neuroinvasion
>
> *Id.* at page 25, col. 1, third paragraph (emphasis added).

Aguzzi further discloses that skilled artisans look to mouse models when evaluating specific aspects of prion disease in other mammals:

> Does a chronic subclinical disease or a permanent carrier status occur in *ruminants* or in *humans*? *Evidence that such a carrier status may be produced* by the passage of the infectious agent across species *was first reported* by Race&Chesebro *and has been confirmed by others, at least for the passage between hamsters and mice*. Chesebro reported that mice inoculated with hamster prions lived a long symptom-free life and did not accumulate detectable PrPSc. PrPSc negative mouse brains were then injected into naive mice, which had no clinical disease for >650 days. The brains of the latter mice were then passaged to hamsters and resulted in rapid lethality.
>
> *Id.* at page 22, col. 1, last bridging paragraph (emphasis added).

Here, it was established that in evaluating carrier status in ruminants and humans, skilled artisans first looked to mouse models. The reliance on mouse models, as mentioned above, is due to the significant similarity between prion pathology across species lines as well as the homology of prion-related proteins amongst various animals.

That mouse models are particularly informative and valuable in the study of prion disease in other animals is supported by the discussion in Aguzzi of challenges facing prion research. Aguzzi states:

> A major challenge in studying various prion strains from cattle, sheep, goats, or humans is to find the appropriate, sensitive recipient bioassay, in which the respective strain of interest...can be propagated. In most cases, prion transmission of distinct species (e.g., human prions into hamster) is restricted by the species barrier, preventing the characterization of, for example, human or ovine prion strains in mouse models. *Therefore, prionologists expressed PrP^C proteins of various species in transgenic*

> *mice to enable transmission or adaptation experiments. This worked very well in many instances of autologous PrP expression, for example, ovine or human PrP.*
>
> *Id.* at page 30, col. 2, last paragraph (emphasis added).

In conclusion, Aguzzi provides ample evidence that: **i)** the underlying prion disease pathology is similar in mammals, including mice, ruminants, and humans; **ii)** the protein responsible for prion disease is a highly conserved protein; and **iii)** based on these principles, skilled artisans routinely rely on mouse models to evaluate prion disease in other mammals.

Finally, an *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. MPEP § 2164.02. If the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Examiner has evidence that the model does not correlate (*id.*, emphasis added). Even with such evidence, the Examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as *reasonably* correlating to the condition. As demonstrated by Aguzzi, it is well known in the art that mouse models of prion disease correlate to prion disorders in other animals. Accordingly, a skilled artisan would not be required to conduct undue experimentation in order to *reasonably* conclude that the recited compositions could be used to stimulate an immune response against prion disease in the claimed animals.

B. Specification Provides Adequate Guidance in view of Knowledge in the Art

The Examiner contends that the specification does not set forth "sufficient teachings" that would allow a skilled artisan to use the claimed compositions to treat or prevent prion disease. The Examiner states that the specification fails to establish effective dosages or methods of administration of the claimed vaccine compositions, and that "the specification provides no description and exemplification of how to use the pharmaceutical composition, without undue experimentation." *See* Office Action, pages 5-6.

In contrast to the Examiner's position, the specification sets forth adequate guidance that would allow a skilled artisan to make and use the claimed invention. Specifically, the specification sets forth the use of a conjugated prion protein composition for mucosal administration, including components of the composition and its manufacture (*see* Example 1). The specification further outlines the use of a prion protein composition wherein the prion protein is generated from recombinant plasmids in transformed bacteria, and wherein the compositions are mucosally administered (*see* Example 2). Example 3 discloses how a skilled artisan would optimize mucosal immunization protocols to achieve optimal immune responses to the claimed compositions. Finally, Example 4 provides an actual working example wherein these concepts are implemented to successfully induce an immune response using compositions encompassed by the present claims.

Furthermore, the Examiner's assertions that the specification fails to provide "effective dosages" or "methods of administration of a vaccine" are not well founded. The specification teaches, for example, that dosages "can contain about 0.5 μg to about 1 mg of each prion protein or conjugate per kg body weight" (*see* published specification, ¶ 62). This disclosure would provide a skilled artisan with reasonable guidance for dose determination. The specification also provides disclosure via mucosal administration (¶ 49), oral administration (¶ 66); intranasal administration (¶ 77); and gastric administration (¶¶ 79, 83, 88, 92, and 95).

In addition to disclosure relating to dosage and administration highlighted above, the specification further teaches the utility of the mouse model for testing the compositions(¶ 72), protocols for peptide or antibody preparation (¶ 73), means to assess efficacy (¶¶ 74-76), and means of administering the claimed compositions to wild populations such as deer and elk (¶ 79).

Applicants point out that many aspects of dosing, administering, evaluating the efficacy of the claimed compositions are also well known to persons of ordinary skill in the art (*see, e.g.*, ¶¶ 72, 73, 77). The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent *coupled with information*

known in the art without undue experimentation (MPEP § 2164.01) (emphasis added). The information that the Examiner contends is missing from the disclosure, such as routes of administration and dosing parameters, is both adequately disclosed (as set forth above) *and* well known in the art. A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, (Fed. Cir. 1991).

C. Specification Discloses Scientific Data and Working Embodiment

The Examiner states that a skilled artisan would have to resort to undue experimentation due to a "lack of scientific data and working embodiments regarding the therapy and prevention of prion diseases" (*see* Office Action, page 7).

In contrast to the Examiner's position, the specification discloses data relating to a mouse model wherein mucosal immunization of mice using a composition encompassed by the instant claims resulted in improved survivability of mice when exposed to scrapie, a prion disease, compared to controls (*see* Example 4 and Figs. 2 and 3). The results of the two experiments disclosed in Example 4 revealed a "highly statistically significant" survival of vaccinated mice. The specification further states that "this approach [used in the mouse experiments] can be translated very easily to an oral vaccine for use in deer or cattle" (*see* specification, ¶ 99]. Thus, the specification discloses *both* scientific data supporting the claimed compositions *and* actual working embodiments demonstrating efficacy of the claimed compositions.

The experimentation required to satisfy the enablement requirement, in addition to not being undue, must not require ingenuity beyond that expected of one of ordinary skill in the art. *In re Angstadt*, 537 F.2d 489, 502 (CCPA 1976). In *Tabuchi v. Nubel*, 194 USPQ 521 (CCPA 1977), a screening procedure that took 15 calendar days was not considered undue experimentation because the test was both simple and straightforward and because of its demonstrated success in producing the desired result.

Based on the data presented in the specification, a person of ordinary skill in the art would be able to make and use the claimed invention with *at least* a reasonable expectation of success. In fact, in view of the experimental data, a person of ordinary skill in the art would instantly realize that the compositions of the instant application have a therapeutic and preventative effect against prion disease in mammals. Here, like in *Tabuchi*, the tests required to determine efficacy of the claimed compositions for treating and/or preventing prion-associated diseases are also simple and straightforward. The only experimentation required would be to evaluate corollary immune responses and survivability in deer, elk, sheep, or cattle after mucosal vaccination with the claimed compositions. Such experiments, even if they are time consuming and costly (due mainly to the size of these animals), would be simple/routine in nature for a person of ordinary skill in the art, would not require ingenuity beyond that expected of a skilled artisan, and therefore, would not constitute *undue* experimentation. Also, Applicants reiterate that an extended period of time to observe an effect, if required, is not an adequate basis to assert undue experimentation as long as adequate guidance is provided. *In re Colianni*, 561 F.2d 220, 224, (CCPA 1977).

For at least the reasons set forth above, the instant specification provides ample guidance for a person of ordinary skill in the art to make and use the claimed invention. Therefore, Applicants respectfully request that this rejection be withdrawn.

* * *

Claim 28 has been rejected as allegedly lacking enablement. The Examiner states that the particular *Salmonella* strains recited in claim 28 would be required to practice the invention, and that the particular strains are not publicly available (*see* Office action, pages7-10).

Because no claims have been found to be allowable, and because of the expense involved in making biological deposits, Applicants respectfully request that this rejection be held in abeyance until one or more claims are found to be allowable (*see* 37 C.F.R. § 1.804(a)). Should allowance occur, Applicants will make an acceptable deposit of the biological organisms

encompassed by one or more allowed claims in accordance with the relevant rules (*see* 37 C.F.R. § 1.809(b)(1)), should such claims exist at the time of allowance.

Anticipation Rejections

Claims 1-3, 9, 38, and 39 have been rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Publication 2003/0219459 ("Bachmann"). According to the Examiner, Bachmann discloses compositions that include a mammalian prion protein (including the elk prion protein), and an adjuvant (*see* Office Action, page 11).

Claims 2, 38, and 39 have been canceled without prejudice or disclaimer. Therefore, this rejection is moot as to these claims.

Without conceding the validity of the rejection, independent claims 1 and 20 have been amended to call for compositions comprising a mammalian prion protein and an antigen carrier or delivery vehicle, wherein: **i)** the mammalian prion protein is selected from bovine, deer, elk, and sheep; **ii)** the composition is suitable for mucosal administration; and **iii)** the composition elicits a humoral immune response that is predominantly associated with a mucosal IgA response and any concomitant immunoglobulin counterpart in other bodily fluids when introduced to a mammalian mucosal immune system. Support for these features is found in the claims as originally filed, and throughout the specification, for example, at ¶¶ 26, 27, 49, and 50.

A claim is anticipated only if each and every element set forth in the rejected claim is disclosed in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628 (Fed. Cir. 1987). Bachmann does not teach or suggest a composition comprising one or more prion proteins wherein the composition is suitable for mucosal administration and induces a predominately IgA immune response when introduced to the mucosal immune system. Thus, Bachmann does not anticipate the present claims. Applicants therefore respectfully request that this rejection be withdrawn.

Obviousness Rejections

Claim 4 has been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Bachmann in view of Benkirane, et al., *J. Bio. Chem.*, 268:26279-26285 (1993). According to the Examiner, Benkirane discloses that D-residues significantly increase the antigenicity of antigenic peptides and lead to high levels of IgG_3 antibodies (*see* Office Action, page 12). The Examiner concludes that it would have been obvious to a person of ordinary skill in the art to make a vaccine composition using peptides composed of D-amino acids (*see* Office Action, pages 11-12).

Claims 9 and 10 have been rejected as obvious over Bachmann in view of U.S. Patent Nos. 6,440,423 ("Clements") and 6,585,975 ("Kleanthous"). The Examiner contends that Clements teach CT-B as an effective adjuvant, and Kleanthous discloses the covalent attachment of CT-B to antigenic proteins (*see* Office Action, page 13). Clements also discloses oral (i.e., mucosal) vaccines that simulate IgA and IgM antibody responses (*see* Clements, col. 1, lines 35-38).

Claims 20-22, 28, and 45 have been rejected as allegedly obvious over Bachmann in view of U.S. Patent No. 5,733,760 ("Lu") and Chabalgoity, et al., *Vaccine*, 19:460-469 (2000). According to the Examiner, Lu teaches vaccine compositions that include attenuated *Salmonella* vectors that express heterologous DNA viral antigens. The Examiner concedes that Lu does not teach the specific bacterial strains recited in instant claim 28. The Examiner relies on Chabalgoity as disclosing that heterologous antigens expressed in LVR01 elicit humoral and cellular immune responses in animals (*see* Office Action, page 15).

Finally, claims 23 and 46 have been rejected as obvious over Bachmann in view of Lu and Benkirane. The Examiner contends that Bachmann and Lu disclose vaccines that include attenuated *Salmonella typhii* transfected with a vector capable of expressing mammalian prions, and Benkirane discloses the use of D-amino acid peptides to improve antigenicity. The Examiner concludes that it would have been obvious to provide a composition that induces immune

responses wherein the antigenic peptides are composed of D-amino acids (*see* Office Action, page 17).

Claims 21 has been canceled without prejudice or disclaimer. Therefore, this rejection is moot as to this claim.

For a claim to be obvious under U.S. patent law, the Examiner must explain why the difference(s) between the prior art and the claimed invention would have been obvious to one of ordinary skill in the art. Additionally, the Patent Office must articulate the reason(s) why a skilled artisan "would have recognized" that combining the prior art "would have yielded nothing more than *predictable* results" (*see* Examination Guidelines, Department of Commerce, *Federal Register*, 72(195):57529 (October 10, 2007) (emphasis added).

The present invention calls for compositions that include a prion protein and an adjuvant or delivery vehicle wherein **i**) the prion protein is selected from bovine, deer, elk, and sheep; **ii**) the composition is suitable for *mucosal* administration; and **iii**) the composition elicits a humoral immune response that is predominantly associated with a mucosal IgA response when introduced to the mucosal immune system. The object of the invention, generally, is to provide a composition that is easily administered to wild animals, and that induces a an immune response predominantly associated with a mucosal IgA response in the gut of a mammalian subject that has been administered the composition by mucosal exposure.

It is well known in the art that difficulties exist in successfully inducing active immunity against prion diseases using conventional compositions due to the immune tolerance against self-antigens, such as prion proteins. The claimed compositions overcome these past failures by successfully providing immune protection against prion diseases, such as scrapie, by eliciting a humoral immune response that is predominantly associated with an IgA response when the self-antigen prion protein is introduced to the mucosal immune system.

The cited references, including Bachmann, do not teach or suggest the selective stimulation of IgA upon mucosal administration by the claimed compositions. The cited

references also do not suggest that the claimed method would be successful in view of the fact that self antigens are used, which as stated above, are well known to demonstrate immune tolerance. In fact, Bachmann states that "the immune system usually fails to produce antibodies against self-derived structures" (*see* Bachmann, ¶ 13).

Thus, in view of the references cited by the Examiner, a person of ordinary skill in the art would not have had a reasonable expectation of success in using compositions that include a prion protein and an adjuvant suitable for mucosal administration to selectively induce an IgA response. In other words, the instant claims would have been unpredictable to a skilled artisan reading the cited references, either alone or in combination, because they would not have predicted that mucosal administration of the claimed compositions would result in the claimed invention, i.e., selective induction of an IgA response, as demonstrated in Example 4 of the specification. In this regard, i.e., that the claimed invention was not predictable, Applicants note that the Bachmann references cites articles authored by Zinkernagel (*see* Bachmann, ¶¶12, 13) who was a 1996 Nobel Laureate for his work in immunology.

For at least the foregoing reasons, the cited references, either alone or in combination, would not have rendered the presently claimed invention obvious to a person of ordinary skill in the art. Therefore, these rejections should be withdrawn.

Conclusion

In view of the above remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining that the Examiner believes can be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: April 28, 2008

Respectfully submitted,

By____/Thomas H. Burrows Jr./_____

Thomas H. Burrows, Jr.
Registration No.: 60,463
DARBY & DARBY P.C.
P.O. Box 770
Church Street Station
New York, New York 10008-0770
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant